Please replace the paragraph at page 11, lines 14-24 with the following paragraph:

B3

--Automating selection greatly diminishes human error in the actual pipetting and biological manipulations. While programming the robot is often not a trivial task, and can be time consuming, automated selection is far faster and more efficient than manual selection. The scientist's time is thus put to better use preparing samples and analyzing data, rather than performing the actual selection. Additionally, automated selection may include real-time monitoring methods (e.g., molecular beacons, TAQMAN®) into the selection procedure and software that can make intelligent decisions based on real-time monitoring.--

Please replace the paragraph at page 14, lines 6-11 with the following paragraph:

B4

--It has been shown that ribozyme catalysis can be modulated by allosteric effectors. In yet another embodiment of the present invention, these allosteric ribozymes, also referred to as aptazymes, are displayed in arrays to be used for monitoring the presence of various molecules, be they inorganic or organic (e.g., metabolites or proteins).--

Please replace the paragraph at page 14, lines 12-22 with the following paragraph:

B5

--For example, aptazymes are anchored to a substrate, such as wells in a multi-well plate, and different ribozyme ligases are covalently immobilized on beads in the wells. Mixtures of analytes and fluorescently tagged substrates are added to each well. Where cognate effectors are present, the aptazymes will covalently attach the fluorescent tags to themselves. Where aptazymes have not been activated by effectors, the tagged substrates are washed out of the well. After reaction and washing, the presence and amounts of co-immobilized fluorescent tags are indicative of amounts of ligands that were present during the reaction.--

Please replace the paragraph beginning at page 15, line 14 with the following paragraph:

B6

--Nucleic acids are generally less robust than antibodies. However, modified nucleotides may be introduced to the aptazymes that substantially stabilize them from degradation in environments such as sera or urine. Similarly, antibodies generally have higher affinities for analytes than do aptamers, and by inference aptazymes. However, the analytical methods of the present invention do not rely on binding per se, but only on transient interactions. The present invention requires mere recognition rather than actual binding, providing a potential advantage of aptazymes over antibodies. That is, even low affinities are sufficient for activation and

B6 cont'd

subsequent detection, especially if individual immobilized aptazymes are examined (i.e., by ligand-dependent immobilization of a quantum dot).--

Please replace the paragraph beginning on page 23, line 15 with the following paragraph:

B7

--In addition to containing introns, genomic forms of a gene may also include sequences located on both the 5' and 3' end of the sequences which are present on the RNA transcript. These sequences are referred to as "flanking" sequences or regions (these flanking sequences are located 5' or 3' to the non-translated sequences present on the mRNA transcript). The 5' flanking region may contain regulatory sequences such as promoters and enhancers which control or influence the transcription of the gene. The 3' flanking region may contain sequences which direct the termination of transcription, post-transcriptional cleavage and polyadenylation.--

Please replace the paragraph beginning on page 32, line 21 with the following paragraph:

B8

--As used herein, the term "selectable marker" refers to the use of a gene that encodes an enzymatic activity and which confers the ability to grow in medium lacking what would otherwise be an essential nutrient (e.g., the HIS3 gene in yeast cells); in addition, a selectable marker may confer resistance to an antibiotic or drug upon the cell in which the selectable marker is expressed. A review of the use of selectable markers in mammalian cell lines is provided in Sambrook, J. *et al.*, *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, New York (1989) pp.16.9-16.15.--

Please replace the paragraph beginning on page 35, line 18 with the following paragraph:

B9

As used herein, the term "probe" refers to an oligonucleotide (*i.e.*, a sequence of nucleotides), whether occurring naturally as in a purified restriction digest or produced synthetically, recombinantly or by PCR amplification, which is capable of hybridizing to another oligonucleotide of interest. A probe may be single-stranded or double-stranded. Probes are useful in the detection, identification and isolation of particular gene sequences. It is contemplated that any probe used in the present invention will be labeled with any "reporter molecule," so that it is detectable in any detection system, including, but not limited to enzyme (*e.g.*, ELISA™, as well as enzyme-based histochemical assays), fluorescent, radioactive, and luminescent systems. It is not intended that the present invention be limited to any particular detection system or label.--

Please replace the paragraph at page 36, lines 10-15 with the following paragraph:

B10

--As used herein, the term "target" when used in reference to the polymerase chain reaction, refers to the region of nucleic acid bounded by the primers used for polymerase chain reaction. Thus, the "target" is sought to be sorted out from other nucleic acid sequences. A "segment" is defined as a region of nucleic acid within the target sequence.--

Please replace the paragraph at page 38, lines 1-12 with the following paragraph:

B11

--With PCR, it is possible to amplify a single copy of a specific target sequence in genomic DNA to a level detectable by several different methodologies (e.g., hybridization with a labeled probe; incorporation of biotinylated primers followed by avidin-enzyme conjugate detection; incorporation of ^{32}P-labeled deoxynucleotide triphosphates, such as dCTP or dATP, into the amplified segment). In addition to genomic DNA, any oligonucleotide sequence can be amplified with the appropriate set of primer molecules. In particular the amplified segments created by the PCR process itself are, themselves, efficient templates for subsequent PCR amplifications.--

Please replace the paragraph at page 40, lines 12-16 with the following paragraph:

B12

--The following examples illustrate the present invention in the *td* gene system of T4. For a full understanding of the examples, refer to Figures 2a and 2b. The examples are provided for illustrative purposes and do not limit the scope of the present invention or the scope of the appended claims.--

Please replace the paragraph beginning at page 41, line 14 with the following paragraph:

B13

--A PCR reaction containing 1 µl of the extension dilution, 500 mM KCl, 100 mM Tris-HCl, (pH 9.0), 1% TRITON® X-100, 15 mM $MgCl_2$, 0.4 µM of GpIWt1.75: 5' –GAT AAT ACG ACT CAC TAT AGG GAT CAA CGC TCA GTA GAT GTT TTC TTG GGT TAA TTG AGG CCT GAG TAT AAG GTG-3' (SEQ ID NO:3), 0.4 µM of GpIWt4.89: 5' –CTT AGC TAC AAT ATG AAC TAA CGT AGC ATA TGA CGC AAT ATT AAA CGG TAG CAT TAT GTT CAG ATA AGG TCG TTA ATC TTA CCC CGG AA-3' (SEQ ID NO:4), 0.2 mM each dNTP and 1.5 units of Taq polymerase (Promega, Madison, WI) was thermocycled 20 times under the following regime: 94° C for 30 seconds, 45° C for 30 seconds, 72° C for 1 minute. The PCR reaction was precipitated in the presence of 0.2 M NaCl and 2.5 volumes of ethanol and

but B13 cont'd

then quantitated by comparison with a molecular weight standard using agarose gel electrophoresis.--

Please replace the paragraph at page 42, lines 5-16 with the following paragraph:

B14

--The aptazyme construct was transcribed in a 10 µl high yield transcription reaction (AMPLISCRIBE™ from Epicentre, Madison, WI). The reaction contained 500 ng PCR product, 3.3 pmoles of P^{32} (α-32P)UTP (3000 Camel), 1X AMPLISCRIBE ™ transcription buffer, 10 mM DTT, 7.5 mM each NTP, and 1 µl AMPLISCRIBE ™ T7 polymerase mix. The transcription reaction was incubated at 37° C for 2 hours. One unit of RNase free-DNase was added and the reaction returned to 37° C for 30 minutes. The transcription was then purified on a 6% denaturing polyacrylamide gel to separate the full length RNA from incomplete transcripts and spliced products, eluted and quantitated spectrophotometrically.--

Please replace the paragraph at page 43, lines 3-9 with the following paragraph:

B15

--The reactions were terminated by the addition of stop dye (10 µl) (95% formamide, 20 mM EDTA, 0.5% xylene cyanol, and 0.5% bromophenol blue). The reactions were heated to 70° C for 3 minutes and 10 µl was electrophoresed on a 6% denaturing polyacrylamide gel. The gel was dried, exposed to a phosphor screen and analyzed using a Molecular Dynamics PHOSPHORIMAGER™ (Sunnyvale, CA).--

Please replace the paragraph at page 45, lines 7-21 with the following paragraph:

B16

--The RNA (10 pmoles/70 µl H_2O) was heated to 94° C for 1 minute then cooled to 37° C over 2 minutes in a thermocycler. The splicing reaction (90 µl) contained 100 mM Tris-HCl (pH 7.45), 500 mM KCl and 15 mM $MgCl_2$. The reaction was immediately placed on ice for 30 minutes. GTP (1 mM) was added to the reaction (final volume of 100 µl) and the reaction was incubated at 37° C for 20 hours. The reaction was terminated by the addition of 20 mM EDTA and precipitated in the presence of 0.2 M NaCl and 2.5 volumes of ethanol. The reaction was resuspended in 10 µl H_2O and 10 µl stop dye and heated to 70° C for 3 minutes and was electrophoresed on a 6% denaturing polyacrylamide gel with CENTURY™ Marker ladder (Ambion, Austin, TX). The gel was exposed to a phosphor screen and analyzed. The unreacted RNA was isolated from the gel, precipitated and resuspended in 10 µl H_2O.--

Please replace the paragraph at page 46, lines 2-15 with the following paragraph:

B17

The RNA (5 µl of negative selection) was heated to 94° C for 1 minute then cooled to 37° C over 2 minutes in a thermocycler. The positive splicing reaction (45 µl) contained 100 mM Tris-HCl (pH 7.45), 500 mM KCl, 15 mM $MgCl_2$ and 1mM theophylline. The reaction was immediately placed on ice for 30 minutes. GTP (1 mM) was added to the reaction (final volume of 50 µl) and the reaction was incubated at 37° C for 1 hour. The reaction was terminated by the addition of stop dye, heated to 70° C for 3 minutes and was electrophoresed on a 6% denaturing polyacrylamide gel with CENTURY™ Marker ladder. The gel was exposed to a phosphor screen and analyzed. The band corresponding to the linear intron was isolated from the gel and precipitated and resuspended in 20 µl H_2O.--

Please replace the paragraph at page 46, lines 17-22 with the following paragraph:

B18

The RNA was reverse transcribed in a reaction containing 250 mM Tris-HCl (pH 8.3), 375 mM KCl, 15 mM $MgCl_2$, 0.1 M DTT, 0.4 mM of each dNTP, 2 µM GpIMutG.101 and 400 units of SUPERSCRIPT™ II reverse transcriptase (Gibco BRL, Rockville, MD). The cDNA was then PCR amplified, transcribed and gel purified as described above.--

Please replace the paragraph beginning on page 50, line 22 with the following paragraph:

B19

--Figure 5 is a diagrammatic representation of one embodiment of the exogenous or endogenous activation of Group I intron splicing. A gene of interest 10 is fused to a reporter gene 12 such as luciferase or beta-galactosidase, which also contains the Group I intron (td) 14. Splicing-out of the Group I intron is induced by an endogenous effector molecule 16, which may be a protein, e.g., Cyt18. Alternatively, splicing-out of the Group I intron may be induced by an exogenous effector molecule 18. Activation of the aptazyme and auto-excision of the intron results in expression of the reporter gene encoded protein 20 that is detected by, e.g., fluorescence 22 or any other desired detectable reaction. The use of a reporter gene 12 of this embodiment may be suitable for use in eukaryotic systems.--